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ARCHIVES OF PEDIATRICS

A MONTHLY DEVOTED TO THE

DISEASES OF INFANTS AND CHILDREN

JOHN FITCH LANDON, M.D., Editor

LEADING ARTICLES IN THIS NUMBER

Drug Therapy in Cerebral Palsy.

Hans Mautner, M.D. 351

Torticollis Resulting from Upper Respiratory Infections, Particularly Sinusitis.

Edward E. Brown, M.D., F.A.A.P. 382

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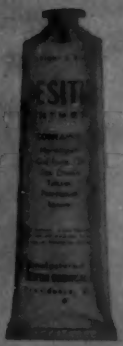

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DRUG THERAPY IN CEREBRAL PALSY

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Wrentham State School,
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Cerebral Palsy is not a disease, but comprehends a series of conditions of different etiologies and different pathologies. In general, we call cerebral palsy those conditions of brain damage which are present at early infancy and are connected with motor disturbances. Drugs cannot correct tissue damage of the brain. We can only combat some of the sequellae of cerebral palsy. We will discuss three conditions which are connected, more or less often, with cerebral palsy, namely, epileptic fits, motor disturbances and mental deficiency.

I. EPILEPTIC SEIZURES

Drug treatment of epilepsy is one of the gratifying chapters of modern medicine. Epilepsy occurs with nearly any localization of damage to the brain. Some special forms, such as Jackson epilepsy, are the result of localised brain damage; other forms may or may not be connected with proven brain damage. Electroencephalography has enabled us to identify, to some extent, clinical types, but not etiological types, especially the petit mal seizures. Undoubtedly some epileptics do not belong to the group of cerebral palsy, such as the 35 per cent of patients with hereditary epilepsy (Groves[1]).

Penfield and Jasper[2] make the following etiological classification of epilepsy:

A. With demonstrable cerebral lesions:	Produced by:
1. Expanding lesions	Neoplasma, chronic abscess, etc.
2. Cerebral cicatrix	Trauma, infection.
3. Local cerebral atrophy	Compression, anemia, infection.
4. Local microgyria	Infantile compression or ischemia.
5. Brain cyst	Vessel closure or hemorrhage.
6. Diffuse cerebral disease	Degeneration, infection, sclerosis.
7. Diffuse cerebral vascular disease	Arteriosclerosis, syphilis, etc.
8. Miscellaneous	Congenital lesions, etc
B. Without demonstrable cerebral lesions:	
1. Centrencephalic (idiopathic)	Abnormal cerebral physiology.
2. Toxic and febrile	Extracerebral causes.
3. Hypoglycemia	Extracerebral causes.
4. Miscellaneous	Angioneurotic, circulatory arrest, etc.

Penfield and Jasper divide the epileptic seizures into the following groups:

a. Motor seizures.
b. Sensory seizures—aurae.
c. Visceral seizures.
d. Psychical seizures.

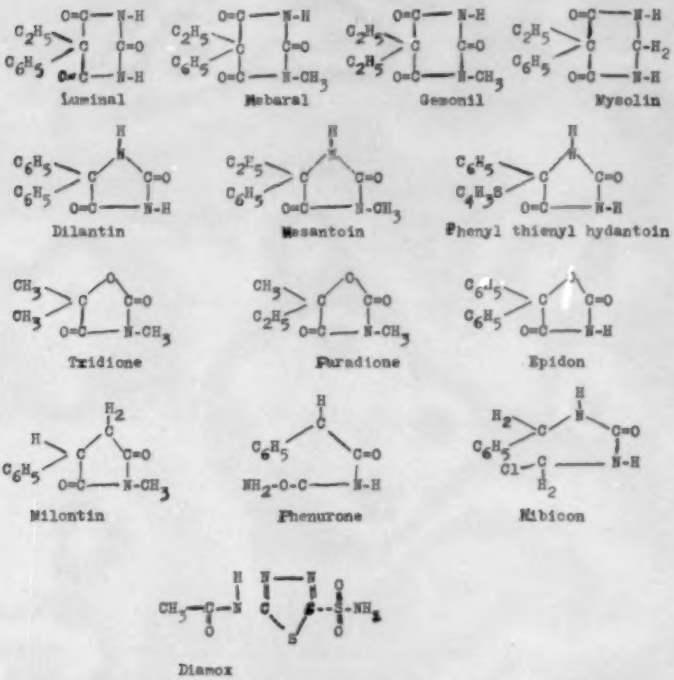
The most important type in cerebral palsy is the grand mal attack, the generalised motor seizures. Psychomotor and petit mal attacks occur also though not as often in cerebral palsy patients. The type of epilepsy depends chiefly on the localisation of the damage in the brain. Psychomotor epilepsy is connected for the most part with localisation in the temporal lobes; petit mal attacks are connected with subcortical midline lesions. Sometimes the various types occur, alternately, in the same patient.

Therapy for epilepsy is not restricted to drug treatment. Some physicians (Peterman[3], Keith[4]) prefer the ketogenic diet to any other treatment, particularly for the complete lack of danger. Surgery also plays an increasingly active role. Penfield[2] recommends craniotomy only when there is reasonable evidence of an intracranial pathological leison. Krynauw[5] recommends extensive operative procedure (hemispherectomy). Permanent healing is assumed to result from surgery and is, therefore, considered over any drug treatment.

Bromides. Bromides were introduced for treatment of epilepsy

by Locock[6] in 1857. In general, they act by replacing chlorides in the body and, therefore, are increased in activity by a low chloride diet. Prolonged treatment leads to depression and very often to severe rash. The toxic symptoms disappear quickly as a rule when bromides are withdrawn.

FORMULAE OF ANTIEPILEPTIC DRUGS



Bromides are given in the few cases where other drugs have failed. Livingston and Pearson[7] recently again stressed their usefulness and effectiveness especially in children with organic brain lesions, and, therefore, in cerebral palsy accompanied by epilepsy. They claim also that toxic symptoms in children are not common. The dose daily is 1-6 grams, depending mainly on the patient's weight. If this daily amount is insufficient to control the seizures, larger doses are useless.

Barbiturates: Phenobarbital or luminal. Luminal was the first of the barbiturates used in epilepsy treatment, and was introduced by Hauptmann[8] in 1912. It remains one of the most reliable drugs and the most often used in epilepsy therapy, especially in combination with hydantoin derivatives. It is relatively well tolerated in young children, but higher doses are often necessary to completely control fits in children. Kramar and Varga[9] in 1936 examined the sedative and anticonvulsive effect in a large number of children and found practically no difference between oral or rectal application, and little difference between phenobarbital and its water soluble sodium salt. They obtained sleep with the following doses:

	Absolute dose in mgm.	Relative dose to body weight in mgm.	Effective after dose, in minutes	Sleep for minutes
First half year	0.057	9.2	43	103
Second half year	0.077	8.4	39	118
Infants	0.12	7.56	109	140
School children	0.15	4.9	155	120

The anticonvulsive dose for nurslings was as follows:

	Absolute dose in mgm.	Relative dose to body weight in mgm.	Start of effect in minutes
First half year	0.142	20.9	30
Second half year	0.150	20.7	78

Treatment starts generally with 0.1 gram, and increases weekly to 0.4 gram. Children younger than four years of age need and tolerate relatively high doses according to their weight. Rashes and drowsiness occur. Penfield and Jasper call it "in many respects the safest and most reliable of anticonvulsant drugs available. Its chief drawback is its hypnotic action." Paradoxical hyperactive effects have been observed in some children, possibly, more frequently among brain injured patients[10].

Mephobarbital, mebaral or prominal. Mebaral was introduced for the treatment of epilepsy by Hyde[11], Blum[12] and Weese[13] in

1932. Its action is less sedative and it is, therefore, preferred by some physicians, especially for active, intelligent patients. This was stressed by Henderson[14], Millman[15], Berris[15a] and others. Cohen, Shestik, and Meyerson[16] have used the combination of mebaral with dilantin with excellent results. Paradoxical hyperirritability is infrequent.

The effective dose is sometimes higher than that of luminal, the initial dose usually is 0.2 grams, and this is probably the reason it is not used more universally. The adult dose ranges from 0.2 to 0.5 grams. A combination of mebaral with dilantin is available as melroin in tablets containing 90 mgm. of mebaral and 60 mgm. of dilantin.

Methabarbital or gemonil. Gemonil was introduced by Butler[17] as an antiepileptic drug. It is especially recommended for seizures in organic brain diseases. It is not only less sedative but also less effective than luminal. The dose is the same as that of mebaral.

Mysoline or primidone. Mysoline was introduced as an antiepileptic by Handley and Stewart[18] and by Bogue and Carrington[19]. Many reports advocating its use were published by Greenstein and Saphirstein[20], Butler [21], Doyle and Livingston[22], Merritt and coworkers[23]. Smith and Forster[24] claim that it comes closest to being an all purpose anticonvulsant, although Greenstein and Saphirstein have seen petit mal seizures increased in mysoline therapy.

The average adult dose is 1 gram daily. Effective control may be obtained with half of this amount; for some, however, the dose has to be increased to as much as 2 grams a day. It is necessary to start with a small dose and increase it very slowly to the full therapeutic dose.

Blood diseases have not been described, but drowsiness, nausea and vomiting, ataxia, mental dullness, and rashes occur. It is not a true barbiturate, lacking one C=O group, but differs also from the hydantoin ring.

Hydantoin derivatives. The hydantoin ring differs from the barbiturate ring in that it lacks one C=O group. The first of these compounds used in medicine was nirvanol, introduced for treatment of chorea minor. It produces, rather regularly, a morbiliform rash after 2-2½ weeks of treatment[25]. If administra-

tion of the drug is discontinued, the rash disappears and simultaneously the chorea fits cease. Nirvanol, taken over a period of time, has caused granulocytoses and its use has been abandoned. It has no anticonvulsant properties. By replacing the ethyl group of nirvanol with a phenyl group, dilantin is formed.

Diphenyl hydantoin or dilantin. Dilantin was introduced for the treatment of epilepsy as a result of experiments made by Merritt and Putnam[26], who examined a long list of drugs for the depression of electrically induced fits in cats. Dilantin was the most effective and least toxic drug on their list. Its sodium salt is water soluble. Many papers have been published about the usefulness of dilantin by Hoff and Jahn[27], Heller and Sloane[28], Lowry[29], and others. Kimbal and Horan[30] claim that they achieved complete recovery in 50 per cent of their patients, some relief in 25 per cent and only 25 per cent did not show any change. Its effectiveness in epilepsy is not connected with sedation, as overdosage induces excitement rather than sedation.

The dosage has to be the smallest amount possible to overcome epileptic fits. We start usually with 0.1 gram, increasing the dose by 0.1 gram daily, up to 0.4-0.6 gram. It is recommended that children under 6 years start with 32 mgm., older children with 0.1 gram.

The effect of dilantin is increased when combined with luminal or mebaral, even in rather small amounts. This combination is the most often used treatment of grand mal and psychomotor attacks. It is a relatively safe medication, inasmuch as blood diseases have rarely been seen, but malignant erythema bullosum, gastric distress, ataxia have been described. The most specific complication is swelling of the gums, seen in young people only, which does not develop on toothless gums. This is seldom so severe that treatment has to be shifted to other drugs. It is not given for petit mal attacks, which it may aggravate.

Mesantoin or methyl-phenyl-ethyl hydantoin. Mesantoin is another drug of the hydantoin group, a methylated nirvanol. It was introduced by Loscalzo[31]. Its usefulness was confirmel by Lennox[32], Kosol[33], Marburg and Helfand[34]. Claims have been made regarding its usefulness in petit mal attacks. Butler[35] says that it is demethylated in the body, a dilantin-like product probably the effective agent.

The average dose is 0.3-0.8 gram daily, starting with 0.1 gram three times daily with increment of 0.1 gram weekly.

Drowsiness, agranulocytosis, aplastic anemia and severe rash (erythema bullosum) have occurred. Regular white blood count is imperative.

Preganon. Preganon or 3 ethyl-5-phenyl hydantoin was introduced as anticonvulsant by Schwabe, Richard and Everett[35A]. It is useful in grand mal and psychomotor seizures, and sometimes in petit mal. The dose for adults is 2-3 gram daily, for children 0.5-1 gram. It is claimed to be non-toxic.

Phenyl-thienyl-hydantoin. This hydantoin compound has been considered by Peterman[36] at least as effective as dilantin. The dose is the same as with dilantin. Toxic symptoms have not been observed.

Oxazolidine derivatives. These drugs contain a ring differing from the hydantoin ring by substituting oxygen for a N-H group.

Tridione or trimethyloxazolidine was chemically produced by Erlenmayer[37] in 1938. It was introduced as an anticonvulsant by Perlstein and Andelman[38], but only became popular when Lennox[39] described its singular effectiveness in petit mal attacks, while deYoung[40] acclaims its usefulness in psychomotor seizures.

The general dose is 0.3 gram three times daily, increasing it slowly to 1.5-2.5 gram. Children under 2 years are given 0.15 gram with increment of 0.15 gram (Jahr and Merritt[41]).

Unfortunately, this drug, most effective for petit mal, is not without danger. Caciulli and Tedeschi[42] have observed a fatal, acute pancytopenia. Also fatal aplastic anemia occurs (Harrison Johnson and Ayer[43], MaKay and Gottstein[44]). A less dangerous complication is photophobia which often can be overcome by dark glasses. Nephrosis also has been described following tridione treatment. A mild harmless drop of leucocytes is often seen in these patients, however, treatment must be discontinued when the white cell count approaches 1500. Regular blood examination is absolutely necessary in tridione therapy.

Paradione or paramethadione. Paradione is a phenylated tridione. It was introduced for antiepileptic treatment by Everett and Richards[45]. It has the same effects as tridione but is claimed to be less toxic. The dose does not differ from that of tridione. Jahr and Merritt recommend a combination of tridione with paradione, so that both could be given in smaller doses. Patients who are sensitive to tridione often can tolerate paradione.

Blood diseases have occurred and regular blood examinations, therefore, are necessary.

Epidon or diphenyl tridione. Epidon, introduced for antiepileptic therapy by Ellerman[46], is claimed to be one-fifth as toxic as dilantin. The average daily dose for adults is 3-5 gram in four doses.

Other drugs. Milontin is a succinamide derivative, differing from the hydantoins by the loss of one N group. It was introduced for treatment of epilepsy by Handley and Stuart[47] in 1952. Zimmerman[48] and Millichap[49] have verified its usefulness in petit mal attacks. Smith and Forster[50] compared its effect with that of mysoline and found it specifically effective in petit mal as well as in psychomotor attacks. They claimed that grand mal attacks are benefited at the start of treatment, but recur even under large dosage. They also observed that children with cerebral palsy became more alert, quieter and better behaved under milantin treatment, but without change in I.Q. It lacks sedative effects. Blood diseases have not been observed, but rash and drowsiness occur. The average dose is 2 gram daily.

Phenurone or phenyl acetylurea. Phenurone is chemically a broken-up hydantoin ring. It was introduced by Spielman, Geissler and Close[51]. Its usefulness was confirmed by Gibbs, Everett and Richards[52], Keith[53] and others. It is recommended primarily for patients refractory to other drugs. It seems to act in any type of epilepsy.

Serious side reactions occur in at least 5 per cent of the patients. Weakness and anorexia are common, and blood dyscrasias, hepatitis, jaundice, and rash also have been observed. Its use, therefore, cannot be generally recommended.

The minimal effective dose is 0.5 gram three times daily; the average daily dose, 2.5 gram; the maximal dose 4 gram.

Hibicon or N-benzyl-beta-chloro propionamide. Hibicon, chemically, is a broken-up hydantoin ring. It was introduced as anticonvulsant by Harand[54]. It is recommended for treatment of grand mal as well as psychomotor seizures. Rashes have been observed, but no blood disease. The dose is 0.5 gram three times daily, increasing if necessary, up to 1.5 gram three times daily.

Meprobamate, miltown or equanil. Meprobamate has been introduced for treatment of muscle relaxation and will be discussed

together with the other drugs acting on muscle conditions. It is mentioned here, because Perlstein[55] has found it of great benefit in the control of petit mal, particularly of the idiopathic variety; it may also have some benefit in treatment of tense forms of cerebral palsy, but it occasionally aggravates grand mal. Its advantage over tridione or paradione lies in its relatively innocuous nature. The dosage used generally is 100-400 mgm. 2-4 times daily.

Acetazolamide-Diamox. Diamox is an antiepileptic drug treatment on a very different base.

Some 30-40 years ago, there was extensive speculation regarding the etiology of tetany, the condition with lowered threshold for peripheral nerve stimulation. Hydration as well as alkalosis were proven to be related, but Freudenberg stated that the discussion of the primary effect of hydration or alkalinization is similar to the query "who was here first, the hen or the egg." Dehydration and acidosis go hand in hand. In the same field, the calcium-phosphorus relationship to these two conditions was discussed. Today, a similar discussion is going on about the low threshold for excitation of the epileptic brain. Hydration unquestionably plays an important role. Water retention under pituitrin with intensive water intake elicits fits in potential epileptics (McQuarrie and Peeler[56]). Also therapeutic effects of acidosis by use of a ketogenic diet as well as acidifying drugs have been observed. The discussion regarding the role of ions has changed from the calcium-phosphorus balance to a sodium-potassium equilibrium with respect to the epileptic brain.

Cohen and Cobb[57] have described the action of prontosil as inhibition of the enzyme carbon anhydrade. Then, another inhibitor of this enzyme was introduced, acetazolamide or diamox. It acts throughout the body, wherever this enzyme is active, especially in the stomach and kidneys. Here it immediately renders the urine alkaline and increases water secretion and loss of sodium. Carbon anhydrase is present in the brain. Its usefulnes in epilepsy, therefore, could be the result of dehydration and alkalinization, primarily by its action on the kidneys, though it could have a direct effect on brain metabolism as well.

Lombroso and coworkers[58], Ansell and Clarke[59] and others report favorable results in nearly every type of epilepsy with diamox, the latter recommending 3-14 mgm. per kilogram of body weight.

They claim that the results are better in idiopathic epilepsy than in cerebral palsy. The toxicity is low. This new treatment for epilepsy, still in the experimentation stage, will undoubtedly be helpful in epilepsy, refractory to other drug therapy.

CONCLUSIONS

In summary, we state that to date no drug devoid of danger and reliably effective in the treatment of any type of epilepsy as yet has been found. The action of the many antiepileptic drugs is not the same, since some act on grand mal seizures only, others on petit mal attacks. Some metabolic changes in epilepsy are known. We mentioned hydration. Loss of intracellular potassium seems to be constant, etc., but the relation to drug therapy is unknown.

Toman and Goodman[60] see three possibilities in antiepileptic action:

1. Action upon non-neural lesions. This may play an indirect role in some conditions by change of blood supply and oxygen tension, but is not probable as a common denominator.
2. Action upon the abnormally altered neurones, to prevent their excessive discharge.
3. Action upon normal neurones to prevent their detonation by excessive discharge.

They consider the last, the most probable, and this is also stressed as the most probable action of anticonvulsant drugs by Unna.[61]

II. DISTURBANCES IN LOCOMOTION

Cerebral palsy may be connected with different types of locomotor disturbances. Denhoff, Holden and Silver[1A] found that 70 per cent of these conditions are spasticity, 14 per cent athetosis, 12 per cent ataxia and 4 per cent rigidity. We find more or less spastic paresis of one or more limbs. Sometimes a high degree of spasticity of all the voluntary muscles is present, including the face muscles with speech impairment. Other patients show increased movement of the voluntary muscles, with tremor or athetosis. Also, variations and combinations of these mean types occur.

The type of disturbance depends mainly on the localization of the damage to the brain. The damage may occur before, at, or after birth. Infections as well as injuries are responsible for after birth damage. Cerebral palsy may be caused by trauma as well as

erythroblastosis due to incompatibility of the blood groups of mother and child. According to Groentoft[2A], birth trauma in full term babies particularly causes hemorrhages with and around the torn tentorium, whereas in prematurely born children more often damage to the vena terminalis and destruction of more medially located brain tissue occurs. Damage before birth may be due to infection or malformation. A rational therapeutic approach is possible only with some understanding of the physiological base of the pathological conditions.

Voluntary contraction of a muscle occurs when a stimulus from the motor area of the cortex reaches the nerve-end plates and muscles by way of the pyramidal tract of brain and spinal cord. Depolarisation is probably the direct cause of muscle contraction and is achieved by the production or liberation of acetylcholine at the nerve endings. This procedure is controlled by different systems. An extrapyramidal system with chiefly inhibitory effect originates in the premotor area, called 4S; it accompanies the cortico-spinal tract for a short part of its course only, diverges from it in the pontil part of the brain stem and reaches extrapyramidal nuclei in the bulb. It is connected to the bulbar reticular formation. Stimulation of this area in decerebrated animals leads to loss of all tone of rigidly extended legs. This system is connected with the reticulo-spinal tract, which when damaged causes spasticity. Magoun and Rhines[3A] have proven the relation of this system to spasticity by control of the stretch reflexes and describe spasticity as an exaggeration of spinal stretch reflexes. Voluntary movements and especially skilled movement are controlled by the cerebellum, which cooperates with the cortex as well as with the brain stem (Peele[4A]).

In 1882, Brehmer[5A] showed that voluntary muscles are innervated by myelinated as well as by non-myelinated nerves; it was thought that the spinal nerves are myelinated and instigate movement and tetanic contractions, whereas the non-myelinated nerves are sympathetic and responsible for the muscle tone. Especially de Boer[6A] has shown the importance of the sympathetic nervous system for muscle tone. But Jansma[7A], as early as 1915, claimed that all animal experiments with regard to muscle tone could be explained by the assumption of a cortical regulating center; Magoun and coworkers[8A] have proven the control of the autonomic nervous system by the reticular system of the hypothalamus

and its relation to muscle tone. Autonomic drugs, therefore, play an important role when we try to influence hypertonic and spastic muscles.

A very different point of view about lasting contractions was taken by H. H. Meyer[9A]. Muscle activity is connected wtih metabolic changes, electric currents, and fatigue. It is known that some shells have muscles for opening which in action have all these properties. But the closing muscles stay contracted without metabolic or electric changes and remain contracted for a very long time (Parnass[10A]). Froehlich and Meyer[11A] have proven that tetanus toxin acts on the spinal cord and not peripherally, and that tetanus is, at least in part, such a condition, without energy production, electric currents or fatigue. They interpret this condition not as contraction but as a setting of the muscle length and muscle tone at another level. Lasting contraction of voluntary muscles without energy or electric changes, etc. was shown by Link[12A] in spastic patients. Such conditions, therefore, are also possible in human muscles. Severely spastic patients do not show the increase of basal metabolic rate which we see in athetotics. These conditions have not been examined recently with newer, more reliable methods.

Clinical pictures of locomotor disturbances differ according to the site of the lesion. Damage to the motor centers or the pyramidal tract leads to more or less spastic paralysis of one or more limbs. A positive sign of Babinski is usually present. Diffuse spasticity of all the voluntary muscles connected often with temors or ataxia is the result of damage of the extrapyramidal system, from 4S to brain stem and spinal cord. It may or may not be combined with damage to the cerebellum, which influences muscle tone, as well as coordination and skilled movements. Increased involuntary movements, as in athetosis, occur by damage of basal ganglia. Drugs may interfere with these conditions by action on different levels, on the brain, spinal cord or peripheral.

We are able to interrupt spasticity or abnormal movement by interruption of the stimuli at the muscle nerve transmission. Curare is the best known drug for the location of such action. Curare, the arrow poison of the South American Indians, acts, as Claude Bernard has shown one hundred years ago, on the nerve muscle junction; nerve as well as muscle remain responsible, the connection only is interrupted. The effect is explained as a

blocking action preventing the normally produced acetylcholine from instigating depolarization at the nerve-end plate. The preparations in use are tubocurarine chloride and dimethyl-tubocurarine iodide.

Another alkaloid of similar action is erythroidine. Both curare as well as erythroidine have been used by Burman[13A] to counteract spasticity. He found some effect lasted for one to two days, "a help to some extent." His best results were obtained in distonia musculorum deformans. James and Braden[14A] also used curare for the treatment of spastic paresis, injecting 0.02-0.1 gram four or five times daily and described relaxation from four to seven hours. Toxic reactions were seen when the dose was 0.08 gram or more, such as drooping of eyelids, general weakness, but no severe reactions or difficulties in breathing occurred.

Curare and curare-like acting drugs are very much in use in surgery as well as in combination with shock therapy when a short action only is desired. The chief disadvantage in its use for spasticity is the short duration of effective action and the fact that curare acts by injection only and not by oral administration. This lack of effect by oral administration was of highest interest to the natural scientists since curare became known. It depends principally on its slow absorption and prompt urinary excretion. The urine contains active curare after any administration of the poison. The slow absorption can be overcome by insulin which increases absorption so that oral application in insulin shock acts as strongly and nearly as quickly as a subcutaneous injection (Koref and Mautner[15A]). Unfortunately, a combination of curare poisoning with an insulin shock treatment cannot be recommended for human therapy.

The short action of curare can be overcome when it is administered in oil (Schlesinger[16A]) but this method is not very practical in human diseases. The high toxicity of curare would not be a contraindication since the effects can be terminated promptly by effective antidotes. Rothberger[17A] has shown the counteraction of prostigmine to curare. Wilson and Wright[18A] described the anticurare action of potassium, and Luisada and Mautner[19A] found that asphyxia overcomes the vagus paralysis of curare, probably by liberation of intracellular potassium.

Some artificial curare-like acting drugs are used in surgery and psychiatry. Some of them seem to act by the same mechanism as curare, some act on another phase of muscle contraction, prevent-

ing the repolarization of the nerve-end plate. No one has proven its usefulness in cerebral palsy. The best known of these are mytolon, flaxedil, anectine, syncurine, succinylcholine chloride or quelicin, and frenquel.

Autonomic drugs. The importance of acetylcholine in muscle contraction and the relation of muscle activity and muscle tone to the autonomic nervous disease renders the action of "autonomic" drugs important in pathological muscle conditions.

Prostigmine or neostigmine, a drug of "parasympathomimetic" action, has been introduced by Kabat and Knapp[20A] for relaxation of muscle spasm in poliomyelitis. They used, primarily, a combination of prostigmine and its contra-acting atropine and claim that atropine prevents all the undesirable side effects of vagus stimulation but does not interfere with the muscle effect, which they relate to spinal synapses. Good results with large doses of prostigmine in spasticity have been published by many authors (Fox and Sparkus[21A], Trommer and Cohen[22A], Jepson[23A] and others). Best results were obtained on spastic muscles in rheumatic arthritis, etc. Perlstein and Barnett[24A] could not find any favorable effect in cerebral palsy. They carefully examined a series of patients under prostigmine and placebo treatment respectively, and stressed the fact that some good results are probably on a psychic basis only.

Atropine, its levo rotatory isomere hysocyamine and the related scopolamine are antagonists to acetylcholine and parasympathetic stimuli. These drugs play a role in the therapy for Parkinsonism and athetosis, and are of help in cerebral palsy of the hyperkinetic type, with tremors and especially with athetosis.

These drugs have been in our armentarium for muscle diseases for a very long time. It became especially popular, when a plant collector, Raeff, in Bulgary in 1926, reported the complete healing of Parkinsonism of many years standing with vine extract of belladonna root, and the Queen of Italy became interested. Many physicians (Panegrossi[25A], Antolini-Furgoni[26A], v. Witzleben[27A], Vollmer[28A], Price and Merritt[29A] and many others have confirmed the usefulness of this treatment in Parkinsonism. The last authors report great improvement in about 47 per cent, moderate improvement in 45 per cent and 10 per cent without improvement. All agree that the effect is related to the three atropine alkaloids. The combination of the brain stimulating atropine or hyoscya-

mine with the sedating scopolamine is probably an advantage. A preparation containing approximately 90 per cent of hyoscyamine hydrobromide, 7½ per cent of atropine sulfate and, 2½ per cent of scopolamine hydrobromide is available by the name rabelon. Vollmer claims that the dose in postencephalitic Parkinsonism has to be higher than in arteriosclerotic patients; the average daily dose for the first group is 3.3 mgm., for the latter, 1.86 mgm. Price and Merritt recommended 0.1-0.2 mgm. one to four times daily as an average dose. The results with atropine alone are not too different from those with the combination.

A long list of drugs with atropine-like effects has been used in the treatment of Parkinsonism.

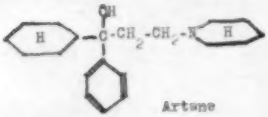
Artane or 3 (N-piperidyl)-1-phenyl-1-cyclohexyl-1 propanol hydrochloride was introduced by Cunningham[30A] and coworkers. Its atropine-like action is strongest in its muscle relaxing effect and weaker in other side effects. It is claimed to improve the conditions in hyperkinetic diseases in 75 per cent without difference between postencephalitic, arteriosclerotic, or idiopathic (cerebral palsy) types. It is given generally in three doses of 1 mgm. daily, increasing slowly up to 6 or even 10 mgm. Severe side effects are rare, but dryness of the mouth, mydriasis, occur though they are for the most part much less severe than those following atropine treatment. Blurring of vision, dizziness, nausea also are common. It has been claimed that mental confusion, agitation, nausea without vomiting occur in approximately 30 per cent of the patients. Blood dyscrasia has not been observed. In our not very extensive experience artane has relieved hyperkinetic, athetotic conditions, but has little influence on general spasticity.

Panparnit, formerly also called parpanit, was prepared by Domenjoz[31A]. It is a diethylamino ethyl-1-phenyl-cyclo pantane-1-carboxylate. The first clinical report of Hartmann[32A] was rather enthusiastic, Carter and Merritt[33A] denied any effect, but Schwab and Leigh[34A] took an intermedial point of view and think that it is often superior to other medications. It has been claimed to have a direct inhibitory effect on voluntary muscles as well as atropine-like inhibition on smooth muscles. It diminishes muscle rigidity in Parkinsonism but effects in a less marked way tremors which sometimes may become more marked than before treatment. Czoniczer[35A] described two patients with spasticity caused by

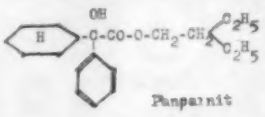
cerebral vascular accidents with good effect of panparnit on rigidity.

Panparnit has to be given in 5 doses daily, but the amount has to be individualized to the needs of the patient. The starting dose is usually 12.5 mgm. five times daily, increasing to 50 mgm. Side effects may sometimes force discontinuance of treatment, particularly vision disturbances as with atropine; nausea and epigastric "burning" are also rather frequent. It has been called a psychotoxic drug, causing an abnormal feeling about the body. Rubber-like knees, micropsia, makropsia and excitement have been observed. (de Boer[36A]).

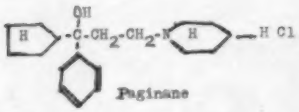
FORMULAE OF DRUGS USED IN MOTOR DISTURBANCES



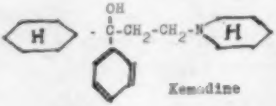
Artane



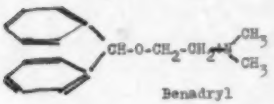
Panparnit



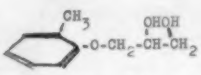
Paginane



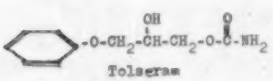
Kemadine



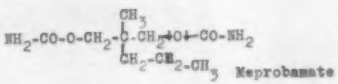
Benadryl



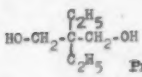
Tolserol



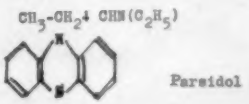
Tolseram



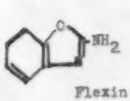
Meprobamate



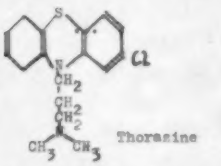
Prenderol



Paraidol



Flexin



Thorazine

Pagitane hydrochloride or *cycrimine hydrochloride* is also chemically related to artane. It is 1-phenyl-1-cyclopentyl-3-piperidine-

1-propanol hydrochloride. Zier and Doshay[37A] used it in combination with hyoscine or benedryl to combat tremors, or with atropine or congestin to combat rigidity. The dose recommended for aged patients is 1.25-2.5 mgm., two to three times daily, for younger adults 2.5-3 mgm. three to five times daily. Dryness of mouth, blurred vision were as common as with atropine. Dow and Smith[38A] found it more effective in idiopathic than in arteriosclerotic patients with Parkinsonism. Magge and DeJong[39A] found it useful in paralysis agitans. It was claimed to be more effective than artane.

Kemadine, also related chemically to artane, has a cyclopentyl in other position. It was introduced for the treatment of Parkinsonism by Schwab and Chafetz[40A] and was claimed to be superior in effect to artane. It may be given in combination with atropine and is effective in alleviating rigidity. The general dose is 2.5-5 mgm.

Benadryl, or beta-diamethyl-amino-ethanol, according to Sherrad, Loew and Schloemer[41A], is the only one of the long list of antihistaminic drugs with atropine-like side effect. Gavack, Elias and Boyd[42A] found it effective in Parkinsonism. Budnitz[43A] has given it, with best results, in a dose of 50 mgm. three to four times daily.

Some drugs introduced for the treatment of Parkinsonism have no atropine-like effects but act on synapses in the cord or brain stem.

Mephenesin, myanesin or *tolserol* is an alpha, beta-dihydroxy-alpha (2 methylphenoxy) propane. Henneman, Kaplan and Unna[44A] have shown that it decreased or abolished facilitation and inhibition reaching anterior horn cells from all levels of the central nervous system. Neural circuits, containing "internuntial" cells are vulnerable to myanesin, whereas direct circuits withstand large doses without effects. The site of action is probably on these internuntial cells. Denhoff, Holden and Silver[45A] have not seen definite, all out improvement with tolserol in cerebral palsy, but the exaggerated reflexes became diminished. Stephen and Chandy claim that it abolished tremor and rigidity or choreatic movements without impairing strength or consciousness. But the effect lasts for seconds, rarely for hours. Berger and Schwartz[46A] introduced oral application. The average daily dose is 3-5 gram. orally or 1 gram. by peroral administration.

Tolseram, the carbamic acid ester of mephenesin, is claimed to keep a more prolonged blood level. It also tests better than tolserol.

The toxic reactions are claimed to be negligible. The average dose is 1-3 gram. three to five times daily.

Meprobamate, equanil, miltown. Meprobamate has been introduced in medicine by Berger[47A, 48A]. It is claimed to be a pronounced muscle relaxant, a potent anticonvulsant and has also a taming effect on monkeys.

It is 2 methyl-2-n propyl-1-3-propanediol discarbamate. Its muscle relaxing action is similar to that of tolserol, but of greater potency and longer duration. Only voluntary muscles are affected. Muscles of the diaphram are relatively insensitive, respiration remains unimpaired. Larger amounts are necessary to influence normal muscle tone than to remove spasm or tremor. Its site of action is the spinal cord and the thalamic region. The toxicity is low. Perlstein[49A] has treated patients with cerebral palsy with meprobamate. Ten of forty-four patients were relieved, especially athetotics. Three of twenty-six athetotic patients were markedly improved, five moderately. Dickel and coworkers[50A] call it valuable for ambulatory treatment of neuro-muscular hypertension. But general spasticity as well as arteriosclerotic Parkinsonism seem to be unresponsive to meprobamate. The dose used in adults is 400 mgm. once or twice daily, but even 4 gram per day seems to be harmless. Drowsiness only has been described as a side effect, however allergic reactions occur. Some patients complain of gastric discomfort.

Prenderol has been examined by Funderburk and Unna[51A]. In contrast to the depressing effect of mephenesin on the brain stem, it is claimed to have a stimulating effect above the spinal level. But it is only one-tenth as effective and of shorter duration in its action than mephenesin. It is 2-2 diethyl.1-3 propanediol.

Parsidol or lysivan was used by Timberlake and Schwab[52A] and by Ziegler and Torres[53A] for treatment of Parkinsonism. It is diethylamino 2 propyl-1-N phenothiamine. It is generally given to adults in a dose of 1 mgm. three times daily or more often. Its toxicity seems to be low. It is called a valuable drug in Parkinsonism, especially for reducing tremors.

Flexin or zoxazolamine is 2 amino-5 chlorobenzoxazole. It was introduced by the firm McNeil. It is claimed to relax hypertensive muscles without interference with normal muscle action. The site of action is probably on spinal synapses. Amols [54A], Kamijo[55A] and others were very satisfied with its effect in spastic conditions,

connected with arthritis, etc. Abrahamson and Baird[56A] used it in cerebral palsy. They found a decrease in muscle tone in all of their twenty-eight children, fifteen with definite clinical improvement. But Rodiquez and Drew[57A] claimed that spasticity resulting from cortical and subcortical disease did not respond as well as spasticity of spinal origin. This conforms with our own observation of the lack of marked response of general spasticity in cerebral palsy. The dose recommended for adults is 250-500 mgm. three to four times daily; for children 250 mgm. can be given two to four times, even to children weighing no more than 5 or 6 kg. Over 10 years twice this amount is claimed to be necessary sometimes. Side effects such as malaise, nausea and vomiting, anorexia, and drowsiness occur. Allergic reactions, urticaria as well as measle-like rashes have been seen and require discontinuance of the treatment.

Chlorpromazine, or thorazine, the so-effective drug for psychotic and overactive, anxious patients, etc. has also been recommended for treatment of spastic condition. Basmaiano and Szatmari[58A] have described complete relaxation of all the voluntary muscles for many hours following intravenous injection of 50 gm. of thorazine. The one adult patient with spasticity in cerebral palsy treated by us in this way immediately fell into deep sleep with loss of muscle tone, a condition which we could not call an improvement of her condition. Some hours later she awoke with very severe spasticity.

Reserpine. Harris and Rowley[59A] examined the effect of the rauwolfia alkaloid reserpine in cerebral palsy. They found it effective for the treatment of tremors and tension athetosis. The dose used for children of approximately 25-30 pounds of body weight was 0.02 mgm.

CONCLUSION

There is a long list of drugs recommended for motor disturbances. Some of them are effective for the treatment of tremors, athetosis and some special forms of spasticity. But a reliable drug of long action for the treatment of spasticity in cerebral palsy has not been found as yet.

III. MENTAL RETARDATION

Approximately half of the children with cerebral palsy remain

mentally retarded (Holden[1B]). Influence on mental development is a much more difficult task than on epileptic fits or spasticity. It is related to the side of brain activity which seems to remain outside of physiological or anatomical research. This dilemma, a part of the body-soul problem, was once described by H. H. Meyer. He said that all the functions of the brain connected with regulation and self-preservation are not questioned as causally determined by our mind. Study of these conditions, cause and their mechanisms will be the aim of physiological research always. But, on the other hand, we are sure of complete liberty to do whatever we intend to do without restriction of causality. These two points of view, the pure and the practical reasoning, according to Kant keep us spellbound in spite of their incompatabilities, holding us with the same invincible force.

These are difficulties comparable to those which Penfield[2B] expressed so well: "How it may be that ganglionic activity is transformed into thinking and how is that thought converted into the activity of conscious voluntary action, we have no knowledge. Here is the fundamental problem. Here physiology and psychology come face to face. We are far from this final understanding, and life is short." These points of view show the difficulties to all problems related to the mind for physiological research.

We have recently witnessed some attempts to peek through this barrier. Mood, a frame of mind, unquestionably seems to be related more to the soul than to the body. Experiments in cats by Hess[3B] have shown that stimulation of some parts of the brain instigates rage and of other points stimulate affection and playfulness.

Another example is mother love. This is considered the strongest working issue of personality, but this characteristic power can be easily influenced or destroyed. A cat injected with estrogen some days before delivery will not care for her off-spring and will let them die of starvation.

The most important finding about brain physiology and its relation to conditions, which were thought to be more on the soul side than on the somatic side is our knowledge of consciousness in regard to specific parts of the brain. This is of great importance in connection with our question of mentality. Consciousness is necessary for learning and mental development. We know that thousands of stimuli reach our central nervous system daily but

only a part of them reaches our conscience and is digested. Only comprehended stimuli have influence on learning and mental growth.

The relationship of the reticular system to consciousness cannot be better presented than by the words of Jasper[4B] who says: "Penfield has been drawn to the necessity of postulating such a system of neurones from his observations upon the effects of local epileptic discharge and epileptic seizures in general as well as from studies of the effect of electrical stimulation of the brain in conscious human subjects." Penfield[5B] has proposed the term "centrencephalic system" for a hypothetical system of neuroses in the brain stem which have equal functional relationship with the two hemispheres and closely interrelated connections with widespread areas of each hemisphere.

From quite a different point of departure, Magoun and his colleagues have found it necessary to postulate about an "ascending reticular system" which is capable of activating the cerebral cortex as a whole. This conception is developed from previous work on the descending reticular system which was shown by Magoun and Rhines[6B] to have such important effects upon spinal reflexes and muscle tone. The ascending reticular system which extends from the medulla to the rostral pole of the thalamus was shown from electrophysiological and behavioral studies to be of importance for the function of the brain as a whole with particular reference to what was termed "arousal" or states of alertness, as opposed to states of inactivity stimulating sleep and unconsciousness. From still another point of departure, Morison and Dempsey[7B, 8B] had previously described a system of neurones in the thalamus, called the interlaminal or recruiting system. Each stimulus of this system of neurones did not evoke specific localized cortical response. Instead, it has the remarkable property of being able to control the electric rhythm of widespread areas of the cerebral cortex in the cat. The studies were confirmed and extended by Jasper and Droogleeven-Fortuyn[9B].

We see the influence of the reticular system on electric changes in the brain. We also learn about the influence on the peripheral autonomic system. It seems probable that some mechanisms of brain activity which are comparable to the function of the peripheral nerves are also related to the function of the reticular system. The peripheral autonomic nervous system is divided into two parts.

The one, termed cholinergic, produces acetylcholine at the nerve endings, the other, adrenergic, produces sympathin, probably norepinephrine. Dale and his coworkers, especially Feldberg[10B], have proven the production of acetylcholine on many synapses of the brain, whereas other synapses are "adrenergic"; the chemical transmitter is not chemically established, but Vogt[11B] has found sympathin, a mixture of epinephrine and norepinephrine, in some parts of the brain. Also the fact that all the drugs are cortical stimulants, which are thought to act by preservation of epinephrine, such as ephedrine, benzedrine, cocaine, seems to prove the importance of sympathin for brain function. Feldberg suggested an alteration of cholinergic and adrenergic synapses in the course of neurones.

We have a long list of substances which are necessary for a normal brain function. This list contains oxygen, glucose, adenosin triphosphate, glutamic acid and many others. Some of them are claimed to be important for the production of acetylcholine. But nothing is known about their relation to mental development.

Glutamic acid is the only one substance which has been used on a wide scale for the treatment of the retarded. Price, Waelsch and Putnam[12B] introduced it in 1943 for the treatment of petit mal and psychomotor seizures and described increased mental and physical alertness as a result of the treatment. Zimmerman and Ross[13B] claimed that rats treated with glutamic acid were learning more quickly in maze experiments than without treatment. The claim to influence mental capacity by any drug was sensational enough to be tried by many physicians around the world. Confirming and opposing publications counter-balance each other. Zimmerman, Burgmeister and Putnam[14B], Albert, Hoch and Waelsch[15B] described significant rise in mental activity. Kane[16B] claimed that good results are seen mainly in brain insulted children and in emotional unrest; Durling and Quinn[17B] reported mild improvement in some patients with different diagnosis. On the other hand, Oldfeldt[18B] and many others could not find any effect.

The cause of these contradictions probably lies in the difficulty of judging behavior, etc. objectively, as Altschul[19B] has explained in detail. Also, the huge quantity of not very pleasant tasting drug necessarily inhibts the general use. But some changes in some patients cannot be completely denied. We[20B] had under observation, at Wrentham, twins with phenylpyruvic oligophrenia, both of extremely low mentality. Both sat quietly throughout the day,

without reacting to any outside stimuli. Even a venepuncture could be done without much resistance. One of them was treated for six weeks with glutamic acid, 15 gram daily. His behavior changed considerably. He did not become brighter but he started to react to outside stimuli, and became very aggressive. A venepuncture was out of the question as he fought against it with all his strength. He attacked his fellow patients, tried to strangle them and was transferred to a State Hospital. We could say that glutamic acid is unable to improve mental development markedly but has some influence on brain function, at least in some patients, with some change in behavior and reactivity. The exact mechanism, of course, is not known. One of the possibilities could be the relation of glutamic acid to acetylcholine production (Nachmansohn, John and Waelsch[21B]).

Autonomic drugs. It seems probable that acetylcholine as well as sympathin (epinephrine as well as norepinephrine) play an important role in brain function. It seemed worthwhile to test whether increased function of these two chemical transmitters have a demonstrable influence on brain activity or even mental development. Acetylcholine as well as epinephrine or norepinephrine are very quickly destroyed in the body. We, therefore, used drugs which are claimed to act by preventing the destruction of these transmitters, ephedrine as the sympathomimetic and prostigmine as the parasympathomimetic drug[22B]. These two drugs have counteracting effects on the heart, intestine, etc., and, therefore can be given together with a minimum of side effects.

The first girl was treated in this way with 15 mgm. of prostigmine bromide and 25 mgm, of ephedrine sulfate. As it happens, this first case has shown by far the best improvement. This 11-year-old girl, the victim of a head accident when she was some months old, in two months improved her I.Q. from 33 to 44, became much more alert and interested in her surroundings. In a larger group of children of different ages and diagnosis, this dramatic result could not be reproduced, but the children were described as more alert and active than prior to the start of the treatment.

Another group of children was treated with the help of Dr. Pirk (Hoffman, LaRoche) receiving two series of tablets. One series contained the above-mentioned amount of both drugs, the other series contained no alkaloid, even in tablets of the same size, color, taste, etc. No one in our institution was informed which

series contained the drugs and which the control. The results in I.Q. determination and in judgment of general behavior by physicians and nurses was sent to Dr. Pirk, who has given us the following anlysis: "Seventeen patients who received the prostigmine-ephedrine combination were classified by you as follows: 5 patients, no improvement; 2 patients, questionable improvement; 2 patients, slight improvement; 8 patients, marked improvement. On the other hand results in the 11 patients who received placebo tablets were classified by you as follows: 8 patients, no improvement; 1 patient, questionable; 2 patients, slight improvement.

The premedication and postmedication I.Q.s did not change significantly. However, as far as the clinical status of the patients is concerned, the incidence and degree of improvement (greater alertness, increased interest in surroundings and increased responsiveness) in the group which received the active material was definitely greater than in the group which was treated with placebo material. These findings are certainly encouraging."

Two of the markedly improved patients were mongoloids of 1 and 3 years of age respectively; the others, congenital spastics of 30, 30 and 27 years; one postencephalitic of 44 years; one myelomeningocele of 31 years, and, one, injured at birth, 12 years of age. The results are far from excellent but show that alertness and responsiveness of some patients increases. Some autonomic drugs have been used before. Bradley and Bowen[23B] have given benzedrine, in its effect very similar to ephedrine, 10-40 mgm. for 1-4 weeks to 100 children and also observed in some children stimulation as well as behavior improvement.

Thorazine or chlorpromazine is another drug which has been given to mentally retarded children, and it is claimed sometimes has an improving effect. Chlorpromazine, whose chemical formula is given in Chapter II, and its related promazine are both widely used in the treatment of psychoses, and especially in excited, overactive, or overanxious patients.

Reports about some improvement in mental development of mentally retarded children were published by Gatski[24B], Davis[25B], Freed and Peifer[26B]. Bair and Herold[27B] even claim improvement in I.Q. Esen and Durling[28B] have observed 14 hyperactive and emotionally disturbed, mentally defective boys who were treated for 2 months with thorazine. In general, it could be said that four children improved markedly in behavior; one seemed rather

worse, more erratic, in his behavior. Some of these boys were examined by means of the "Funkenstein test"[29B]. Mecholyl in a dose of 10 mgm. was injected and the blood pressure determined for 25 minutes. The two boys who reacted best to thorazine, showed a severe drop in blood pressure, the boy with the adverse reaction showed no change in blood pressure.

Funkenstein, Greenblatt, Solomon[30B], who introduced this test, claim that psychotic and schizophrenic patients who react with severe drop in blood pressure are those who react well to electroshock therapy, whereas patients without strong response to mecholyl are not benefited by the shock treatment.

The relationship of the Funkenstein test to pathological brain function is not quite clear. Gellhorn[31B] claims that the reticular system of the hypothalamic region controls the autonomic system and is pathologically influenced in psychotic patients, who, therefore, for their abnormal regulation of the autonomic system, react strongly to mecholyl. Funkenstein[32B] explains his test with the difference in the reaction to mecholyl because some patients regulate the vagus stimulation by production of epinephrine, others by norepinephrine.

v.Euler[33B] thinks that epinephrine and norepinephrine are produced by different cells. Others claim that everywhere in the body norepinephrine only is produced and changes, when stored, quickly to epinephrine (Beulbring[34B]). This may be the reason for the higher amount of epinephrine in the adrenal medulla compared with the higher percentage of norepinephrine in the peripheral sympathetic nerve endings.

The reticular system as site of action for the chlorpromazine effect has been proven experimentally (Cathala and Pocidallo[35B]) and the ring seems to be closed. But much work remains to be done to achieve an understanding of the relation of these problems to our conception regarding mental development.

Rauwolfia-alkaloids. There is a list of drugs introduced recently for the treatment of psychotic patients. Chlorpromazine is doubtlessly the one which is used most widely. But the rauwolfia alkaloids, promazine, ritalin and anarexin should be mentioned. It seems that up to the present time only the effect of rauwolfia alkaloids on mentally retarded children has been studied. The Indian plant rauwolfia serpentina was introduced in modern medicine for the purpose of reducing blood pressure. Its value in

psychotic patients was found more or less by chance. Different alkaloids have been isolated, reserpine or serpasil being the most frequently used form of treatment. Noce, Williams and Rappaport[36B] treated seventeen mentally retarded patients with 1-2 mgm. of reserpine daily and claim very satisfactory results; four of their patients were completely changed in their behavior, became alert, cooperative and responsive to their surroundings; the others were quieter and slept better. The authors hope that reserpine will be the most important therapeutic development in the history of psychiatry. Jensen[37B], Zimmerman and Burgemeister[38B] also have reported good results with serpasil treatment in special types of behavior problems. Benda[39B] used a special rauwolfia preparation called koglucoid. He also described excellent results with some mentally retarded children. However, the best results have not been with brain injured patients.

The theoretical basis of reserpine effects is not definitely known. It has been claimed to counteract epinephrine (Raymond-Hamot[40B]). It is also known to antagonize serotonin to which it has some chemical relation. The possibilities for the relation of serotonin and reserpine are manifold (Wooley and Shaw[41B], Wilkins[42B]). The physiological role of serotonin is much discussed. It has been called a chemical transmitter.

Tolserol. Freedman, Kremer, Robetiello, and Effron[43B] treated behavior disorders in children with tolserol with good results, even without the presence of a psychosis. They claim that benedryl had even more marked effect.

Milontin. We have mentioned in Part I that Smith and Forster observed that children with cerebral palsy became more alert and better behaved under milontin treatment but without any change in I.Q.

It is always questionable how far such behavior disorders and their improvement are connected with mental retardation. It is difficult to adequately assess objectively the behavior improvement, mental improvement, etc. especially in children who self-evidently in the course of weeks and months learn and develop.

Finally we may say that drug treatment of epilepsy in cerebral palsy is effective, though more research must be done on it. Drug treatment of hyperkinetic disorders is less satisfactory, but in many patients, one or the other of the long list of recommended drugs has proven useful. Drug therapy for spasticity shows some be-

ginning, even though a reliable drug has not been developed as yet. It seems reasonable to be hopeful. The most difficult phase is drug treatment of the mentally retarded. Here we see some more or less promising beginnings in development though the prospects for the near future seem somewhat dim.

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PREMALIGNANT FIBROPITHELIAL TUMORS OF PINKUS AND BASOCELLULAR EPITHELIOMA: BASED ON TWO NEW CASES. R. Degos and J. Hewitt. (Am. dermat. et syph., 82:124-139, March-April, 1955). Two new cases of fibroepithelial tumors bring the number reported to nine, when added to those originally described by Pinkus in 1953 and those identified by him in the literature. The tumors remain benign for long periods of time. They are often multiple. They are often confused with fibromas, seborrheic verrucae, or superficial epitheliomas. Their histology is characteristic, however; it shows an epithelial network that gives rise to basocellular buds and a fibromatous hyperplasia of the dermis. These tumors develop into basocellular epitheliomas and are to be considered a special variety of this lesion. One of the authors' patients had tumors from childhood; this would seem to support the concept of a nevoid, embryonic origin of basocellular epitheliomas.—*J.A.M.A.*

TORTICOLLIS RESULTING FROM UPPER RESPIRATORY INFECTIONS, PARTICULARLY SINUSITIS

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I have seen about one hundred children with acquired torticollis (wry neck) affecting the sternocleidomastoid muscle in the past 25 years, an average of four cases yearly, it is surprising that only rare mention[1, 2, 3, 4] is made of its usual cause, sinusitis. Grisel[2] described this type in 1930 as a "nasopharyngeal torticollis."

Other causative foci in the head, such as tonsillitis[5] and mastoiditis[6] are listed in the literature. For example, Holt and McIntosh[7] stated that in children "acquired torticollis most commonly results from inflammation of the neck as a complication of tonsillitis or pharyngitis." Smith[8] noted the same foci but adds that torticollis frequently follows scarlet fever, measles or diphtheria. Following a nasopharyngitis or sinusitis, an occasional patient may develop torticollis of such severity as to produce atlanto-axial displacement.[6, 9, 10]

Acute wry neck is not an uncommon symptom in older children.[11] The sternocleidomastoid muscle on one side is in a painful spasm.

Fig. 1.

Fig. 2.

Torticollis, left, secondary to sinusitis; head inclined to affected side. Puffs beside nose caused by sinusitis. Note photophobia in #1, and mouth-breathing in #2.

The patient holds the neck rigid in the position of least pain.[12] The head may be inclined to the affected side (Figs. 1, 2) or, more often, to the opposite side.[6, 13, 14] (Figs. 3, 4).

On the affected side, the deep cervical nodes are almost invariably enlarged[4, 11, 15, 16, 17] and tender. The presence of cervical adenitis will often be overlooked unless specifically sought.

ETIOLOGY

Torticollis may be congenital or acquired. Congenital cases are due usually to birth injury.

Acquired torticollis has many causes, the most common of which are upper respiratory infections. Uncommon causes of torticollis are ocular defects, fracture of cervical vertebrae and other traumatism, arthritis, tuberculous cervical adenitis and hysteria.

Allergy may aggravate a chronic sinusitis and precede some cases of torticollis. Randolph[18] believes that allergy per se may produce acute torticollis, but a description of his patients reveals symptoms of sinusitis. He stated that food allergens ingested at night may produce torticollis upon arising, whereas the same foods taken in the morning do not result in torticollis. This curious phenomenon may be explained only by infection in the sinuses. Allergens produce bogginess of sinus mucous membranes[19], rendering these tissues prey to secondary infection,[19, 20, 21] symptoms occurring particularly after recumbency and only in patients with sinusitis.[22]

Sinusitis as Usual Cause: Indirect evidence from the literature and direct evidence from clinical examination point to sinusitis as the usual cause of acquired torticollis. The indirect evidence is first discussed.

Fig. 3. Right torticollis associated with sore throat; head inclined to unaffected side.

Onset of torticollis upon arising. Attacks of torticollis are noted usually upon arising[18, 23] (Figs. 2, 3, 4). Purulent toxic exudates in chronic sinusitis tend to accumulate under pressure during the

night, particularly after prolonged recumbency[22]. Such confined toxins readily enter the cervical nodes[4, 24] and produce numerous symptoms[22]. No other focus of infection shows this striking diurnal variation.

Season and Chilling. Torticollis is seldom encountered in warm weather; almost every acute case occurs in the fall, winter and spring. Watson and Thorn[12] noted that most cases are seen in the colder months. Chilling predisposes to colds or upper respiratory infections in persons with chronic sinusitis and these "colds" often represent acute exacerbations of chronic sinusitis[25]. Chilling and consequent torticollis may result from exposure to drafts[18], wind and cold air[8]. Torticollis may be seen in summer after a swim (Fig. 4), due to chilling and to trauma of the nasal mucous membranes bathed in a hypotonic or hypertonic solution.

Fig. 4a Fig. 4b

#4a: Right torticollis (2nd day); head inclined to unaffected side. Had been immersed in river 3 days earlier, developed sore throat and stiff neck. #4b: One day later, after treating sinusitis.

Preceding upper respiratory infection. At the onset of torticollis, an upper respiratory infection is usually present in the form of tonsillitis, pharyngitis or sinusitis.[4, 6, 7, 9, 10, 12, 26, 27] Recurring pharyngitis and tonsillitis are usually secondary to chronic sinusitis.[28]

Association with contagious diseases. Because sinusitis uniformly complicates such diseases as scarlet fever[29], measles[30] and influenza[31], torticollis may make its appearance during convalescence from any of these diseases. (Fig. 2).

Association with rheumatic fever. Comroe[32] pointed out that muscular rheumatism or fibrositis of the sternocleidomastoid muscle has been associated with acute torticollis. Sachs[11] stated: "Ordinary wry neck, so frequent in children, is due to a rheumatic myositis." I believe the latter statement to be accurate if we interpret "rheumatic" as "streptococcic" and the source of toxins mainly in infected sinuses.[33] At the Cardiac Research Clinic of the New York Post-Graduate Medical School we[34] found that all of our rheumatic children had a chronic sinusitis, and I[33] later concluded that rheumatic fever is caused by streptococci in a chronic sinusitis. It is not surprising that a very stiff neck will sometimes accompany early rheumatic fever.[35] In three patients of Coburn, "torticollis was so severe that meningitis was diagnosed before definite rheumatic manifestations were recognized."[36] The torticollis is secondary to sinusitis and the resulting cervical adenitis.

Direct clinical evidence. History and physical examination almost invariably confirm the presence of chronic sinusitis in children with acute torticollis. History may reveal as many as twenty of fifty symptoms as described by the author in children with chronic sinusitis.[28]

Clinically, one can quickly determine the amount of tenderness of the individual sinuses[24, 37] by palpation and by percussion of the ethmoids, antra and frontal sinuses. In almost every case of torticollis, tenderness of the sinuses and of the cervical nodes is greater on the side of the involved sternocleidomastoid muscle. Following treatment of sinusitis, all three inflamed areas (sinus, lymph node, muscle) decrease in tenderness. Free motion of the head ensues. (Fig. 4B).

TREATMENT

The treatment of acquired torticollis should be directed to the causes noted under Etiology. The child who awakens with a stiff neck will usually reveal tender sinuses and cervical adenitis on the affected side. He may have, in addition, tonsillitis, or, in the absence of tonsils, pharyngitis. In any of the above infections, penicillin is given intramuscularly in single doses of 300,000 units daily for about three days.

One should instill an astringent three times daily, isotonic nose drops (1 per cent ephedrine sulphate in normal saline solution), or, the child may use an inhaler, benzedrex. This is followed by

the application of hot, wet towels to the face for five or ten minutes. Cold creaming the face is advisable before applying the hot towels.

The head should be elevated by placing two four-inch blocks under the head posters of the bed. Prolonged recumbency is to be avoided.[22] During the day the child is placed in a sitting posture, or reclining slightly. At night the sternomastoid muscle may be relaxed by inclining the head to the affected side, supported by an extra, small pillow under the neck and face.

Under this regimen relief is usually obtained in one day. Severe cases may respond on the second or third day.

I have not seen recurrences of torticollis in children who daily treat their chronic sinusitis with nasal astringents, facial hot towels, head-high posture during recumbency, and avoidance of allergens and chilling. All of my cases have been encountered either as new patients or in children who have abandoned the above simple treatment.

CONCLUSIONS

1. Among approximately one hundred children with acquired torticollis seen in the past 25 years, the great majority were caused by an acute exacerbation of chronic sinusitis. Many children had an associated pharyngitis or tonsillitis. All had a cervical adenitis on the involved side.

2. Allergy is not a cause of torticollis, but may predispose to it. Allergens acutely aggravate a chronic sinusitis. Bacterial toxins enter the cervical nodes, particularly during recumbency, resulting in a unilateral stiff neck upon arising.

3. Chilling frequently precedes torticollis by producing an acute flare-up of chronic sinusitis, with or without an associated tonsillitis or pharyngitis.

4. Treatment of the acute sinusitis, as outlined, results in a rapid subsidence of pain and stiffness in the affected sternocleidomastoid muscle, most cases responding in one day (Fig. 4), others usually in two or three days. Simple daily treatment of chronic sinusitis will tend to prevent recurrences of torticollis.

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DEPARTMENT OF ABSTRACTS

Conducted by

MICHAEL A. BRESCIA, M.D., NEW YORK

SINGLETON, E. B.; THOMAS, J. R.; WORTHINGTON, W. W. and HILD, J. R.: PROGRESSIVE DIAPHYSEAL DYSPLASIA (ENGELMANN'S DISEASE). (Radiology, 67:233, August 1956).

Engelmann's disease is a rare disorder of bone characterized by weakness and underdevelopment of the muscles of the extremities and fusiform sclerosis of the diaphyses of the long bones. The previously reported cases are reviewed and an additional case is submitted. The presence of thickening of the vessel walls in the biopsy specimen in this latter case suggests that the disease may be on a vascular basis. AUTHORS' SUMMARY.

FARQUHAR, J. W.: THE SIGNIFICANCE OF HYPOGLYCEMIA IN THE NEWBORN INFANT OF THE DIABETIC WOMAN. (Archives of Disease in Childhood, 31:203, June 1956).

Confirmatory evidence is offered that the blood sugar level falls more profoundly and more rapidly in the infant of the diabetic mother than in the offspring of the normal woman. It is shown that there is no relationship between the development of a morbid neonatal course and the blood sugar level at the time or the extent and rapidity of the fall. It is shown also that there is no relationship between the degree of hypoglycemia or the gradient of the change in levels and abnormal incidents later in the first two weeks of life. It is probable that there is no relationship between the blood sugar changes and subnormal intelligence in later childhood. The administration of glucose may be dangerous and at the least it may serve to postpone the establishment of the correct diagnosis in abnormal infants. AUTHOR'S SUMMARY.

PHILBROOK, F. R. and INGALLS, T. H.: POLIOMYELITIS VACCINATION IN SOUTHEAST MASSACHUSETTS IN 1955. (New England Journal Medicine, 255:385, Aug. 23, 1956).

The experience of more than 4000 children, 6 years through 8 years of age, who had received a single dose of the improved

Salk vaccine in May, 1955, just before a state-wide epidemic of poliomyelitis, was compared with that of nearly 5000 children of the same age who had not received the vaccine. During the epidemic season of approximately four months, the rate for paralytic and bulbar cases was ten to twenty times higher in nonvaccinated than in vaccinated children who had received 1 ml. of the newly released vaccine. AUTHORS' SUMMARY.

ARNOLD, F. A.; DEAN, H. T.; JAY, P. and KNUTSON, J. W.: EFFECT OF FLUORIDATED PUBLIC WATER SUPPLIES ON DENTAL CARIES PREVALENCE. (Public Health Reports, 71:652, July 1956).

The results of the Grand Rapids-Muskegon study, after 10 years of observation, indicate that the adjustment of the fluoride content of a communal water to an optimal level (approximately 1 p.p.m. fluoride) will produce the following effects: 1. A striking reduction in the prevalence of dental caries in the deciduous teeth. At the peak of prevalence, namely, 6 years of age, the caries rate for the deciduous teeth was reduced by about 54 per cent. 2. A marked reduction in the prevalence of dental caries in the permanent teeth. In children born since fluoridation was put into effect, the caries rate for the permanent teeth was reduced, on the average, by about 60 per cent. 3. Some benefit among persons whose teeth having already formed or erupted when fluoridation is begun. 4. No undesirable cosmetic effect from dental fluorosis.

AUTHORS' SUMMARY.

SCORER, C. G.: THE INCIDENCE OF INCOMPLETE DESCENT OF THE TESTICLE AT BIRTH. (Archives of Disease in Childhood, 31:198, June 1956).

Over 1,700 newborn male infants have been examined in a maternity unit in order to find out the incidence of incomplete descent of the testicle. In full-term deliveries it was 3.4 per cent, and in those born prematurely 30.3 per cent. An arbitrary definition of incomplete descent has been made. If this should become standard, the figures produced by different workers would then be comparable. The babies have been classified according to weight. Descent was most common when the baby was between three pounds and six pounds. A follow-up of all cases of incomplete descent showed that in more than 50 per cent the testicle reached the scrotum during the first month of life. AUTHOR'S SUMMARY.

HALPERN, S. R.: RECURRING ACUTE RESPIRATORY INFECTIONS IN CHILDREN. (Southern Medical Journal, 49:890, August 1956).

The successful treatment of recurring acute respiratory infections requires a painstaking study for the underlying etiologic factors by means of history, physical examinations, laboratory studies and observation of the patient. Control of these factors is achieved by such procedures as: (1) allergic management; (2) treatment of the "healthy carrier" in the family; (3) removal from nursery school; (4) improvement of diet; (5) indicated surgery; (6) prevention of chilling; (7) respiratory vaccine; (8) gamma globulin; and (9) the proper use of antimicrobial agents prophylactically and therapeutically. AUTHOR'S SUMMARY.

DARGEON, H. W.: LEUKEMIA IN CHILDHOOD. CURRENT THERAPEUTIC CONSIDERATIONS. (New York State Journal Medicine, 56:2079, July 1, 1956).

The use of new chemical agents for the treatment of leukemia in children has induced tmporary remissions but no cures in this important cause of childhood mortality. Over half of the children now receiving therapy will survive at least one year from the date of clinical recognition of the illness. These powerful and potentially toxic agents must be used with caution. The search for the etiology of leukemia is continuing. Meanwhile, it is suggested that the use of chemotherapeutic agents in lymphosarcoma after the conventional definitive treatment be further explored as to their possible value in preventing leukemia in such patients.

AUTHOR'S SUMMARY

PEERY, T.M.: BRUCELLOSIS AND HEART DISEASE. I. THE SHAKY FOUNDATIONS OF "RHEUMATIC" HEART DISEASE. (Postgraduate Medicine, 19:323, April 1956).

A review of the clinical, bacteriologic, immunologic and pathologic findings raises many doubts that "rheumatic fever" is a single disease. At the present time, there is no procedure of any sort that can positively identify rheumatic fever. Until such time as a diagnostic test for rheumatic fever is available and the problem can be definitely decided, it seems wise to keep an open mind on the question and to investigate thoroughly any reasonable suggestion of a new cause for carditis. Brucellosis is suggested as a likely cause of chronic valvular heart disease. AUTHOR'S SUMMARY.

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